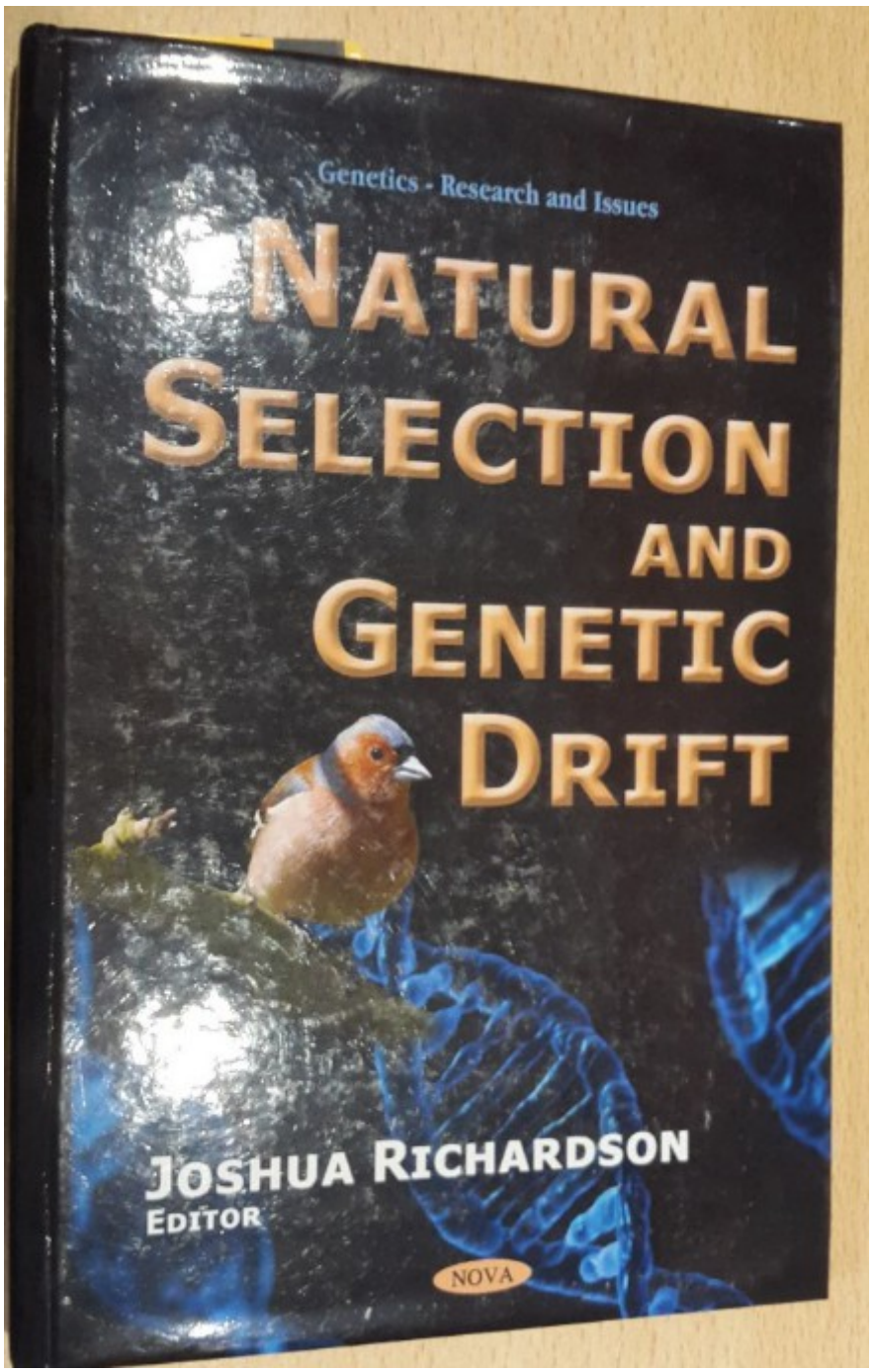
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Chapter 3

GENETIC DRIFT AMONG NATIVE PEOPLE FROM SOUTH AMERICAN GRAN CHACO REGION AFFECTS INTERLEUKIN 1 RECEPTOR ANTAGONIST VARIATION

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ABSTRACT

Genetic variation is generally responsible for ethnic differences in certain diseases, including inflammatory processes. The antagonist of cytokine IL-1, IL-1Ra, has been widely studied among Caucasian and African populations for genetic polymorphisms, and interethnic differences have been documented. However, the variation and genotype distribution of polymorphisms from these genes among South American Amerindians are thus far unknown. We present the results for a VNTR located in the IL-1Ra second intron, in a sample of 169 individuals belonging to 5 Native American populations from Argentina and Paraguay, identified as native according to their self designation, and their geographic location. We also compare this data with the results obtained from a sample of non-native Argentinian people. Among the five known alleles of the VNTR, we found only two (alleles 1 and 2) in the native populations from Gran Chaco, and heterozygosity was 19%.

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The allele 2 which is considered proinflammatory (IL-1Ra * 2) has been found in homozygosity at a considerable frequency among native individuals. However, the association of this allele with inflammatory disease previously demonstrated for other populations of the world, might not be acting in the same way for native people, probably due to local adaptation. This would indicate that the allele 2 will probably not have a negative influence on individuals of native origin who have homozygous genotype 2-2. On the contrary, few records on inflammatory disease are available for the native people.

It seems that the increment on allele 2 is not related to any adaptive process but to genetic drift, that changes randomly the allele frequencies of different genetic regions along the genome. The effect of genetic drift has already been demonstrated with genetic markers located in autosomes, X and Y chromosomes. These results indicate that we must be very cautious when studying populations that passed a process of genetic drift, which can become a confounding factor in epidemiological studies. This information will contribute to a future understanding of the association of this polymorphism with disease, and its incidence in different ethnic groups.

TEXT

The native human populations inhabiting the American territory have arrived to the continent through different migratory events, and have been involved in social and cultural interactions with other human groups. This exchange can be partially reflected in their current genetic structure. However, other processes than genetic flow have played an important role in the microevolutive change of these populations, and genetic drift might be, even nowadays, one of the most important processes acting on them.

Before the arrival of the European colonizers, the Gran Chaco region possessed a rich cultural and linguistic diversity. But the initial contact between Native Americans and Europeans five hundred years ago, initiated a dramatic reduction of the native populations, as happened in other parts of the American continent (Martínez-Sarasola 2004). Many groups were completely wiped out, while others have introduced some genetic admixture from non-native groups (Mulligan et al. 2004) giving rise through the centuries to the current Latin American populations, which share three main ancestral origins: Native American, European, and African (Salzano and Bortolini 2002; Rondón et al. 2008). In this chapter we present the analysis of some extant native groups inhabiting the South American Gran Chaco region, and the

genetic drift process that can be found through genetic analysis. Information on these populations is not always concordant with the conclusions on their origin and history (Torroni et al. 1993; Horai et al. 1993; Zago et al. 1995), in part due to the genetic drift process, which generates a strong differentiation among tribes.

Figure 1. Geographic location of the phytogeographic Gran Chaco region.

The Gran Chaco is a plain, very wide phytogeographic region of approximately 100.000 km^2, which includes part of Bolivia, Paraguay, and northeast of Argentina (Figure 1). About 5.000 years ago it was colonized by several nomadic native groups of hunting, fishing and gathering habits: Abipon, Mocoví, Qom, Mbya, and Pilagá belonging to Guaycurú linguistic

group, Wichí, Chorote, and Chulupí of the Mataguayo linguistic family, and the Lule-Vilela group in the western part, corresponding to current Argentinian territory. In the northeast, the Ayoreo and Lengua, live in the region that belongs to Paraguay. These ethnic groups did not practice written language, therefore the historical record begins with the arrival of Spanish colonizers, and before that moment, information can be obtained only from oral transmitted tales (Martínez-Sarasola 2004; Tissera 2008). These native groups show an important diversity of spoken languages as a result of complex interactions and interchanges (Jurado Medina et al. 2014).

BACKGROUND

Molecular biology offers a wide variety of coding and non coding (neutral) DNA markers for analyzing the diversity among individuals of a population, and among populations of a region. There is a background of information on DNA markers for Gran Chaco populations including several SNPs (single nucleotide polymorphisms), STRs (short tandem repeats, also called microsatellites), and insertions-deletions. SNPs are small changes in the DNA sequence affecting only one nucleotide. Usually, SNP mutation rates are moderate to low. STRs are short sequences tandemly repeated, they are highly variable and highly informative for studying genetic diversity and evolutionary processes. Insertion-deletion markers are sequences that are either present or absent, and can extend from only one or few nucleotides to several hundreds of them. An important amount of information has been obtained from non coding markers in Y chromosome, mitochondrial DNA, autosomes and X chromosome, while much fewer information is available from coding regions, such as blood antigens and HLA genes (Goicoechea et al. 2001; Dejean et al. 2004).

UNIPARENTAL Y CHROMOSOME VARIABILITY

Male specific region of Y chromosome has been widely studied throughout the world, allowing to disentangle the genetic structure of different populations. The diversity of Gran Chaco native people has been analyzed through uniparentally inherited markers localized in Y chromosome, SNP and STR polymorphisms.

For the native populations of Gran Chaco, the search of autochtonous Q1a3a haplogroup has been firstly focused among different Chaco groups to determine either a native or a non-native origin of this chromosome. This haplogroup is determined by M3 SNP marker. Among those considered native, a set of STR markers has been usually genotyped to determine the diversity of each analyzed group.

An analysis on three different ethnic groups, Pilaga, Wichí, and Toba on SNP and STR markers showed genetic drift as a powerful evolutionary force for these seasonal hunters living in small bands (Demarchi and Mitchell 2004). The Native American-specific M3 marker was carried by 76.9% of the individuals, with a moderately high intergroup variation based on Y-chromosome STRs (10.7%).

In this way, two populations of Wichí origin living in Formosa province, 70 kilometers away from each other, were analyzed by Ramallo et al. (2009), showing a frequency of the Q1a3a haplogroup of 72,7% and 81,6%, and a rich lineage variability regionally distributed. Allelic variation was also non coincident. Their nomadic way of life and their habit to live in small groups has been clearly a strong force driving to genetic drift. Moreover, the Wichí people show a distribution of partialities called "Wichí ethnic complex" with certain linguistic differences (Braunstein 2006; Ramallo et al. 2009).

However, a small sample belonging to another ethnic group, did not show such influence. The Mocoví people living south to Gran Chaco, in Santa Fe province, were also analyzed for Y markers including two SNPs (M3 and M346) and ten STRs (Glesmann et al. 2011). The M3-T transition was present in 52% of the individuals, and STR haplotype diversity was 99,69%. In this case, the Mocoví Y-chromosomes still retain an interesting variability, with some of the M3-T haplotypes not found in other Amerindian groups. This considerable amount of haplotype variability is likely to be originary from this population.

X CHROMOSOME VARIABILITY

Due to its particular mode of inheritance, and its lower recombination rate compared to autosomes, the patterns of genetic variation of different types of markers specifically located in the X chromosome can result highly informative for population studies. Indeed, its special characteristics give a chance for analyzing genetic variability from a different point of view (Bourgeois et al. 2009; Ribeiro Rodrigues et al. 2009, 2011).

A study on X chromosome variation was performed including five Chaco ethnic groups: from Argentina, Wichí and Chorote from Salta province, and Mocoví from Santa Fe; from Paraguay: Lengua and Ayoreo (Catanesi et al. 2007). This analysis showed significant differences among these populations, with high Fst and Rst values, probably due to the drift process. The differentiation was related to the geographic location of populations, grouping those from Salta together, and those from Paraguay together, with Mocoví resulting separated from the rest (Catanesi et al. 2007).

A more recent study included another Wichí population living in a region called "Impenetrable" due to its hard climatic conditions and dense vegetation, in the Chaco province, and a Mocoví population (the same that was analyzed for Y chromosome) living in the south of Gran Chaco (Glesmann et al. 2013). A high proportion of homozygotes and a marked linkage disequilibrium was found especially in Wichí, with differences in modal alleles and frequencies between both populations. On the other hand, a higher proportion of variation was observed in Mocoví. It has been reported that the Mocoví people belonging to the studied population are currently taking part of the neighbor non-native society through work and education. This social integration might be responsible for a cultural change among Mocoví (Franceschi and Dasso 2010). Although the genetic flow between Mocoví and non-natives might be occurring (Citro 2006), a more important process of genetic drift may be reflected in the X chromosome variation reported, especially among Wichí. The Wichí people from Chaco province not only live isolated from other native and non-native groups, but also display an irregular distribution in small bands along the territory. Their geographic isolation and the extreme environmental conditions may be considered as the major factors contributing to the population differentiation (Glesmann et al. 2013).

UNIPARENTAL MITOCHONDRIAL VARIABILITY

Native Americans share five different maternally inherited mitochondrial DNA haplogroups: A, B, C, D, and X (Schurr et al. 1990; Torroni et al. 1993; Santos et al. 1996), which are present in different proportions depending on the demographic background of each population (Bailliet et al. 2004; Avena et al. 2012; Wang et al., 2008; Pauro et al. 2010; Yang et al. 2010; Motti et al. 2013). An unbalanced proportion of male and female native uniparental lineages has been clearly described, as a consequence of mixed marriages of European males with native women through the last 5 centuries, thus making

maternal haplogroups of native origin to widespread in different regions (García and Demarchi, 2006; 2009, Pauro et al. 2010; Yang et al. 2010).

Interestingly, a loss of mitochondrial variability has been described for certain Gran Chaco communities, including Wichí from Chaco province and Ayoreo from Paraguay. The random action of genetic drift or a bottleneck effect has been proposed as responsible for this reduction (Demarchi et al. 2001; Demarchi and Mitchell 2004).

AUTOSOME NON CODING VARIATION

Studying different genomic compartments has contributed to the understanding of the evolutionary processes occurring among South American Gran Chaco native populations. Different autosomal STR markers have shown in general a drop in the number of alleles and, consequently, an excess in the proportion of homozygote individuals. Variation in modal alleles for each native population, and a drastic reduction in allele number were found, particularly among Wichí (Tourret et al. 2000; Catanesi et al. 2001). As a consequence of genetic drift, a relatively poor correlation with geographic location of the tribes was more notable when analyzing autosomal variation (Zago et al. 1996; Tourret et al. 2000; Catanesi et al. 2001) than X chromosome variation (Catanesi et al. 2007).

AUTOSOME CODING VARIATION IN THE INTERLEUKINE 1 RECEPTOR ANTAGONIST

Coding genetic variation is generally responsible for ethnic differences in certain diseases. Natural selection changes allele frequencies according to environmental conditions, thus modifying the diversity of a population under selection (Hedrick 2000). Information on coding regions is scarce for native populations from Gran Chaco region, but the HLA region has been reported to present a low variability of dinucletide STRs for three Chaco tribes: Wichí, Chorote, and Toba (Dejean et al. 2004), and metabolic genes have also been studied (Bailliet et al. 2007).

The inflammatory processes can be more prevalent among individuals who belong to a certain ethnic group, thus needing a specific medical treatment. Interleukin-1 (IL-1) is a cytokine secreted by macrophages and

other cell types, playing an important role in the inflammatory response of virtually all cells and organs, as a major pathogenic mediator inducing pain (Dinarello et al. 2012; Gabay et al. 2010; Sims and Smith, 2010; Garlanda et al. 2013). The IL-1 gene family comprises several genes including three closely related IL-1A, IL-1B, and IL-1Ra encoding respectively two proinflammatory cytokines IL-1α, IL-1β, and their natural antagonist, the IL-1 receptor antagonist (IL-1Ra). The latter blocks IL-1 action by competing for its receptor (Dinarello 2009). The gene coding IL-1Ra maps the long arm of human chromosome 2 (band q14-21) (Steinkasserer et al. 1993; Grover et al. 2006). This gene presents a polymorphic VNTR in intron 2, with an 86 base pair repeated motif responsible for differences in the levels of expression of the receptor, which is reportedly associated with autoimmune diseases, ischemic stroke, and other pathologies (Worrall et al. 2007). The VNTR presents 5 allelic variants corresponding to 2, 3, 4, 5, and 6 copies of the 86 bp repeat (Tarlow et al. 1993; Grover et al. 2006). Three potential protein binding sites are located nearby this polymorphism, therefore the number of repeats may influence the level of gene transcription and posterior translation to a protein product.

Studies on North American U.S. population proposed the association of the allele IL-1Ra*2 of this VNTR with chronic inflammatory processes and pain (Joos et al. 2001; Foster et al. 2004), and this allele has also been associated as a risk factor for various autoimmune diseases (Rider et al. 2000; You et al. 2007; Havemose-Poulsen et al. 2007).

Since genetic diversity at the immune system is primarily important for human population´s survival, the variation of this polymorphism in a group of native people inhabiting the South American Gran Chaco was explored.

A sample of 169 Amerindians from the Gran Chaco region -including Argentina and Paraguay, and a sample of 107 non-Amerindian Argentineans mainly of European ancestry (from Misiones and Buenos Aires provinces, Argentina), were analyzed. The Amerindians, identified as native according to their self designation, and their geographic location, comprised individuals belonging to five native groups from Gran Chaco: Lengua (from Paraguay, n = 36), Ayoreo (from Paraguay, n = 41), Chorote (from Santa Victoria Este, Salta province, Argentina, n = 20), Wichí (also from Santa Victoria Este, n = 39), and Mocoví (from Colonia Dolores, Santa Fe province, Argentina, n = 33). A small sample of 26 non-Amerindian Argentinians of full Japanese ancestry was also genotyped, however this group was not polymorphic for this VNTR, showing only homozygote individuals for allele 4, probably due to the small

number of individuals analyzed, therefore this sample was not included in the comparative analysis.

The VNTR was amplified using the primers Fw: CTCAGCAACACTCCTAT, and Rv: TCCTGGTCTGCAGGTAA, in a MP1-Evo02 Thermocycler (La Plata, Argentina). Cycling conditions included 36 cycles of 94° 40 sec., 57° 1 min., and 72° 1 min., with an initial denaturation of 94° 2 min., and a final extension of 72° 5 min. Alleles were defined in 2% agarose electrophoresis, as in Foster et al. (2004). After post-gel DNA staining with GelGreen™ (Biotium, Hayward, CA), the electrophoretic bands were visualized in an image analyzer GelDocXR (Biorad, USA).

Allele frequencies, gene diversity, exact test of Hardy-Weinberg equilibrium, molecular variance (AMOVA), and pairwise genetic distances measured as Wright index Fst and Rst, were analyzed with Arlequin v. 3.5 (Excoffier et al. 2010). The Fst index estimates the amount of genetic differentiation between populations, by comparing total heterozygosity (five populations together) to each population heterozygosity. Genetic distances were represented using a matrix of distance MDS (multi dimensional scaling) with the program NTSYS 2.1 (Exeter) using Rst Slatkin´s estimation from allele frequencies.

We found three out of the five known alleles of this VNTR (Table 1). The allele 2 was more frequent among the native people than in European and North American populations, and the allele 5 was found only in non-native European ancestry people.

Table 1. Sample size and genotype frequencies observed for IL1-Ra VNTR. Alleles are named by the number of repeats

Population	Sample size	Genotype Frequencies					
		2/2	2/4	2/5	4/4	4/5	5/5
Lengua	36	0.111	0.278	-	0.611	-	-
Ayoreo	41	0.024	0.195	-	0.780	-	-
Chorote	20	0.2	0.1	-	0.7	-	-
Wichí	39	0.205	0.154	-	0.641	-	-
Mocoví	33	0.061	0.182	-	0.757	-	-
Buenos Aires	104	0.038	0.010	-	0.875	0.019	0.058
Misiones	77	0.065	0.078	0.013	0.740	0.013	0.091
Japanese	26	-	-	-	1	-	-

Total native heterozygosity was 19%, while non-native people showed a much lower value, 2,5%. Genotypic distribution did not fit Hardy-Weinberg

equilibrium among Chorote and Wichí Amerindians (Chorote: observed heterozygosity = 0.100, expected heterozygosity = 0.385, P = 0.00278 ± 0.00005; Wichí: observed heterozygosity = 0.154, expected heterozygosity = 0.410, P = 0.00019 ± 0.00001). It is noteworthy that the VNTR did not fit populational equilibrium in two cases, mostly due to the presence of higher frequencies of homozygotes for allele 2 than expected (Table 2). The genotyping of this marker was rechecked for those homozygotes, and such genotypes were confirmed.

Table 2. Allele frequencies for the five Amerindian ethnic groups (frequencies +/-S.D.)

Allele	Mocoví	Lengua	Ayoreo	Chorote	Wichí
2	0.152+/-0.044	0.250+/-0.051	0.122+/-0.036	0.250+/-0,069	0,282+/-0,051
4	0.848+/-0.044	0.750+/-0.051	0.878+/-0.036	0.750+/-0,069	0,718+/-0,051

Pairwise Fst analysis showed significant values for non-native (Buenos Aires + Misiones) compared to native populations, except for Ayoreo, and also between Wichí and Ayoreo (Table 3, data below diagonal). On the other hand, for pairwise Rst estimations non significant values were observed (Table 3, data above diagonal). Rst value between Wichí and non-native gave a limit probability of P = 0,5, showing a tendency to differentiation.

Table 3. Population pairwise Fst and Rst values below and above the diagonal, respectively. Significant results are in bold (α = 0.05)

Population pairwise Rst / Population pairwise Fst	Non-native	Wichí	Chorote	Ayoreo	Lengua	Mocoví
Non-native		0.01555	-0.00278	-0.00242	0.00310	-0.00898
Wichí	**0.12312**		-0.01662	0.06532	-0.01088	0.03460
Chorote	**0.09339**	-0.01662		0.04015	-0.01983	0.01135
Ayoreo	0.00760	**0.06532**	0.04015		0.04112	-0.01008
Lengua	**0.09222**	-0.01088	-0.01983	0.04112		0.01524
Mocoví	**0.01772**	0.03460	0.01135	-0.01008	0.01524	

An analysis of molecular variance (AMOVA) (Table 4) showed a significant 3.77% differentiation between native and non-native people (P = 0.03773).

Table 4. AMOVA Analysis (distance method: Fst). Samples for testing genetic structure were grouped as native and non-native populations. α = 0.05

	Sum of squared	Variance components	Percentage of variation
Among groups	2.143	0.00565	3.77
Among populations within groups	1.443	0.00329	2.20
Within populations	76.869	0.14079	94.03
Total	80.455	0.14973	100

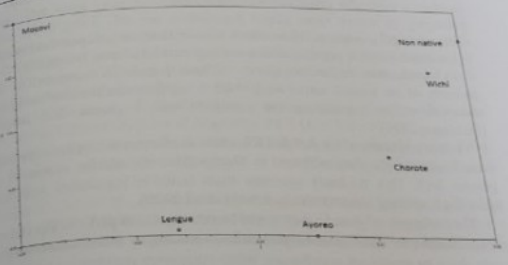

Figure 2. Multidimensional scaling (MDS) obtained from Rst distance matrix (Stress value = 0.0000). Non-native sample includes populations from Buenos Aires and Misiones.

Multidimensional map obtained from Rst distances (Figure 2) did not show any clustering, but the distribution of native populations showed certain agreement with their geographic distribution, with Mocoví (the population in a southernmost location) positioned distant from all other populations, Lengua near Ayoreo, and Chorote near Wichí. It is interesting to remark the close position of Wichí and non-native people, consistent with a migrational

process. However, Fst values suggest the migrational process is more likely occurring among these native populations.

DISCUSSION

The existence of an enormous drift in American native people, acting on small subpopulations and generating variation from one population to another, has been emphasized. The stochastic accumulation of differences through the time often increases differences among populations, while intrapopulation variation decreases enormously (Cavalli-Sforza et al. 1996).

Our results on a VNTR polymorphism within a coding region might be interpreted in different ways. On the one hand, natural selection might be acting on these populations favouring proinflammatory allele 2 in order to increase a particular inflammatory-immune pathway, since many individuals belonging to native Gran Chaco populations are still living under strict environmental conditions. However, it is more likely to interpret these results as the effect of finite population size making variability to be lost rapidly.

The decrease in heterozygosity of each population compared to the diversity of the pooled native sample taken together, and the low variability observed within populations are consistent with a genetic drift process (Holsinger 2015).

When populations are isolated from one another, as it happens especially with *Wichí* people, they will tend to diverge from one another as a result of genetic drift. This tendency operates much faster in populations with few individuals, driving them to divergence (Hedrick 2000).

The influence of genetic drift could be detrimental to perform association genetic studies for specific diseases, because case-control and/or cohort studies might drive to erroneous conclusions when comparing populations which are substructured and in disagreement with Hardy-Weinberg equilibrium (Acosta et al. 2012).

However, the association of this allele with inflammatory disease previously demonstrated for other populations of the world, might not be acting in the same way for native people, probably due to local adaptation. This would indicate that the allele 2 probably does not influence negatively on individuals of native origin who have homozygous genotype 2-2. On the contrary, few records on inflammatory disease are available for the native people (Trujillo Miriam, personal communication). It seems that the increment on allele 2 is not related to any adaptive process but to genetic drift, that

changes randomly the allele frequencies of different genetic regions along the genome. The effect of genetic drift has already been demonstrated with genetic markers located in autosomes, X and Y chromosomes (see above).

These results indicate that we must be very cautious when studying populations that passed through a process of genetic drift, which can become a confounding factor not only in evolutionary studies, but in epidemiological studies. In the first case, it could be considered as a positive selection effect; in the second one, the existence of a genetic association with certain phenotype could be falsely interpreted (Solovieva et al. 2004).

This information will contribute to a future understanding of the association of this polymorphism with disease, and its incidence in different ethnic groups.

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